IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Sherie L. Morrison et al.	Examiner:	M. Zeman
Serial No.:	09/095,385	Group Art Unit:	1643
Filed:	June 10, 1998	Docket:	30435.45USU1
Title:	SECRETORY IMMUNOGLOBULIN PRODUCED BY SINGLE CELLS AND METHODS FOR MAKING AND USING SAME		

DECLARATION OF SHERIE L. MORRISON UNDER 37 C.F.R. § 1.132

I, SHERIE L. MORRISON, declare as follows:

1. I am a named inventor on the patent application identified above, and am authorized by the Assignee to make this declaration.

2. I am Professor and Chair of the Department of Microbiology, Immunology, & Molecular Genetics and a faculty member of the Molecular Biology Institute at the University of California Los Angeles. I have authored more than 175 journal articles published in the field of molecular immunology.

3. As of July 30, 1993, the effective filing date of United States Patent Number 5,534,411 to Weltzin ("the Weltzin patent"), and as of March 28, 1995, the actual filing date of the Weltzin patent, an assertion that immunoglobulin A (IgA) antibodies can be bound to secretory component ("SC") by transfecting IgA-secreting hybridoma cells with an expression vector containing the cDNA for SC, as stated at column 11, lines 39-48 of the Weltzin patent, would not have been credible to those skilled in the art of immunology. This particular statement in the Weltzin patent that is cited and relied upon by the Examiner in the Office Action dated December 8, 1999, would not have provided the skilled artisan with a reasonable expectation of success in the absence of data demonstrating that these IgA-producing cells could in fact successfully assemble and secrete IgA in secretory form following transfection with a nucleic acid encoding SC for the reasons enumerated below.

4. Disclosed in the above-identified patent application are data collected in my laboratory and described in an article by myself and Koteswara R. Chintalacharuvu, who is also a named inventor on the above-identified patent application, which article was published in the June 1997 issue of the Proceedings of the National Academy of Sciences ("PNAS") 94:6364-6368. A copy of this PNAS article is attached as Exhibit 1.

5. Prior to obtaining the data described in the PNAS article of Exhibit 1 and in the above-identified patent application, those skilled in the art of immunology, including myself, had doubts about the ability of cells that do not naturally produce secretory IgA (sIgA) to properly assemble sIgA because of the already known complexities of the natural assembly process. Specifically, sIgA is naturally produced by a transcytotic process in an epithelial cell using a polymeric IgA that has already been assembled with J chain in a plasma cell. In this naturally-occurring process, the polymeric IgA secreted by the plasma cell binds to a polymeric IgA receptor expressed on the basolateral surface of the mucosal epithelium, forming an immunoglobulin-receptor complex. This immunoglobulin bound to receptor is then transcytosed through a complex pathway to the apical surface of the epithelial cell, and during this transit a disulfide bond forms between the IgA and the receptor. At the apical surface, the SC is then cleaved from the transmembrane domain, releasing the IgA-SC complex into external secretions. Until this cleavage takes place at the apical surface, the SC remains in a membrane-bound form. The information set forth in this paragraph is described in the above-identified patent application at page 2, lines 5-14, and in Tamer et al., 1995, The Journal of Immunology 155:707-714, a copy of which is attached as Exhibit 2.

6. The doubts regarding the ability of a single, non-epithelial cell to produce sIgA held by those skilled in the art prior to the publication of the PNAS article of Exhibit 1 were based on a number of variables, including: (1) uncertainty as to whether SC could be bound to polymeric IgA when the polymeric IgA did not enter the cell as an already assembled molecule complete with J chain, as occurs naturally; (2) uncertainty as to whether SC in a soluble form rather than the naturally-occurring membrane-bound form could be bound to the IgA; (3) uncertainty as to whether the naturally-occurring transcytotic process was essential to cellular production of sIgA; and (4) uncertainty as to whether a non-epithelial cell could produce sIgA,

given that the naturally-occurring process takes advantage of the properties and polarity unique to epithelial cells. In addition to these uncertainties regarding individual steps of the sIgA assembly process, the complexities of the assembly process as a whole gave rise to uncertainties about the ability to obtain proper assembly of a sIgA through simply transfecting an IgA-producing cell with a vector encoding SC.

7. As an example of the uncertainty experienced in this art, on September 29, 1998, I received correspondence via electronic mail from Dr. Blaise Corthésy of the Division of Immunology and Allergology of the State Hospital in Lausanne, Switzerland. A copy of this correspondence is attached as Exhibit 3. In this correspondence, Dr. Corthésy indicated that it was the 1997 PNAS article cited above and attached as Exhibit 1 that convinced him that individual cells can be made to perform the "whole job of assembling a whole secretory IgA molecule", and that this method provides "an attractive alternative to the in vitro reconstitution using purified secretory component and dimeric IgA."

8. I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: March 3, 2000

Sherie L. Morrison

Sherie L. Morrison, Ph.D.